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10/038,509	01/03/2002	Terry J. Smith	066742-0015	5468

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SIP_Docket@mwe.com

Office Action Summary	Application No.	Applicant(s)	
	10/038,509	SMITH ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7 and 9-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/06/2009 has been entered.

2. Claims 1, 3-7 and 9-11 are currently pending and under consideration as they read on a method of detecting Graves disease in a patient comprising obtaining a biological sample from the patient and measuring the binding of disease specific IgG with IGF-1 receptor relative to a control wherein an elevated level of IgG IgF-1 binding relative to the control indicates Graves disease.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-7 and 9-11 *stand* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of detecting Graves' disease in a human patient comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient, and (b) detecting fibroblast activation by IGF-1 receptor (IGF-1R) IgG autoantibodies in said orbital or skin sample by measuring IL-16, RANTES or T cell migration towards said fibroblasts in said orbital or skin sample, wherein an increased presence of fibroblasts activated by IGF-1 receptor

(IGF-1R) IgG autoantibodies in said orbital or skin sample compared to control indicates Graves disease; a method of detecting the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) and detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an elevated level of IL-16 detects the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts; a method of detecting the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; and (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANTES detects the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts; a method of detecting the presence of IGF-1 receptor (IGF-1R) IgG autoantibody activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; and (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level of both IL-16 and RANTES detects the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts. The specification does not provide reasonable enablement for : a method of detecting Graves' disease in a patient comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient, and (b) detecting in said orbital or skin sample the activation of fibroblasts by binding of **disease specific IgG to the IGF-1 receptor (IGF-1R)** relative to a control wherein an increased presence of **IgG-activated fibroblasts** compared to the

control indicates Graves' disease and wherein fibroblast activation is determined by measuring the level of **a chemical marker** expressed by said **IgG-activated fibroblasts** or by measuring T cell migration towards said fibroblasts in said orbital or skin sample of claim 1; wherein an elevated level of **the marker** compared to the control indicates presence of said IgG-activated fibroblasts of claim 3; a method of detecting the presence of **antibody-activated fibroblasts**, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an elevated level of IL-16 detects the presence of **antibody-activated fibroblasts** of claim 9; a method of detecting the presence of **antibody-activated fibroblasts**, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANTES detects the presence of **antibody-activated fibroblasts** of claim 10; and a method of detecting the presence of **antibody-activated fibroblasts**, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level of both IL-16 and RANTES detects the presence of **antibody-activated fibroblasts** of claim 11 and as applied to claims 4-7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons as set forth in the Office Action mailed on 06/27/2008.

Applicant's arguments filed on 02/06/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> " While Applicant respectfully maintain that the specification enables the full scope of the claimed invention, the claims have been amended to recite the embodiments indicated in the Office Action to be enabled, rendering moot the rejection. Accordingly, Applicants respectfully request removal of the rejection of claims 1 and 3-11 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention."

It remains the Examiner's position that the specification discloses a method of detecting Graves disease or rheumatoid arthritis in a human patient comprising contacting an antibody sample with a fibroblast sample from the same patient and measuring the IL-16 and/or RANTES levels that are induced by Graves' disease specific IgG activation of the IGF-1R on the fibroblast, whereby increased expression of either cytokine is associated with the presence of disease specific IgG and is an indicator of disease; and a method of detecting Graves disease or rheumatoid arthritis in a human patient comprising: contacting an antibody sample with a fibroblast sample from the same patient; exposing a NWNA-T cell to the activated fibroblast using a Boyden chamber; measuring the T cell migration toward the activated fibroblast, and determining that positive T cell migration indicates IL-16 and/or RANTES expression in disease-specific IgG-activated fibroblasts through their IGF-1R, whereby increased expression of either cytokine is associated with the presence of disease specific IgG.

The specification is not enabled for a method of detecting Graves disease by measuring fibroblasts that are activated by "disease specific IgG to the IGF-1 receptor (IGF-1R)." First, the term "disease specific" is not limited to any particular disease and as such is not enabled for use in detecting Graves Disease. The antibodies must necessarily be Graves' Disease specific to be enabled for use in the claimed invention of specifically detecting Graves Disease. Further, the specification is not enabled for the use of any "IgG to the IGF-1 receptor (IGF-1R)." Rather, the only enabled source of the "IgG to the IGF-1 receptor (IGF-1R)" is the same patient. Therefore, the antibody is an IgG autoantibody to the IGF-1 receptor (IGF-1R). The claims as currently recited may be read to include the additional limitation of activating fibroblasts by binding of Graves Disease specific IgG to the IGF-1 receptor (IGF-1R). However, since the claims are limited to disease detection in patients that are the source of the fibroblasts, the enabled method does not actually require IgG to the IGF-1 receptor (IGF-1R) at all. Rather, the method only requires fibroblasts that have been activated by IgG autoantibody to the IGF-1 receptor (IGF-1R) in vivo or in vitro. A method which reads on any IgG to the IGF-1 receptor (IGF-1R) is not enabled since the disease is detected using the fibroblasts, not the IgG to the IGF-1 receptor (IGF-1R).

It remains the Examiner's position that the specification does not disclose a method of measuring any "chemical marker expressed" by fibroblasts to detect fibroblasts activated by IgG autoantibody to the IGF-1 receptor (IGF-1R). The specification discloses only the measurement of RANTES and IL-16 as chemical markers of fibroblast activation. The term "chemical marker" encompasses a broad genus of indicators of fibroblast activation that don't necessarily

have anything to do with Graves Disease such as increased expression of surface molecules or other normal cellular indicators of growth and differentiation.

The specification is also not enabled for a method of detecting "antibody activated" fibroblasts. The specification is enabled for the detection of Graves Disease specific IgG to the IGF-1 receptor (IGF-1R) activated fibroblasts.

5. Claims 1, 3 and 6-7 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method of detecting Graves' disease in a human patient comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient, and (b) detecting fibroblast activation by IGF-1 receptor (IGF-1R) IgG autoantibodies in said orbital or skin sample by measuring IL-16, RANTES or T cell migration towards said fibroblasts in said orbital or skin sample, wherein an increased presence of fibroblasts activated by IGF-1 receptor (IGF-1R) IgG autoantibodies in said orbital or skin sample compared to control indicates Graves disease; a method of detecting the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) and detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an

elevated level of IL-16 detects the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts; a method of detecting the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; and (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANTES detects the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts; a method of detecting the presence of IGF-1 receptor (IGF-1R) IgG autoantibody activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; and (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level of both IL-16 and RANTES detects the presence of IGF-1 receptor (IGF-1R) IgG autoantibody-activated fibroblasts.

Applicant is not in possession of: a method of detecting Graves' disease in a patient comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient, and (b) detecting in said orbital or skin sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein an increased presence of IgG-activated fibroblasts compared to the control indicates Graves' disease and wherein fibroblast activation is determined by measuring the level of **a chemical marker** expressed by said IgG-activated fibroblasts or by measuring T cell migration towards said fibroblasts in said orbital or skin sample of claim 1; and wherein an elevated level of **the marker** compared to the

control indicates presence of said IgG-activated fibroblasts of claim 3 and as applied to claims 6-7 for the same reasons as set forth in the Office Action mailed on 06/27/2008.

Applicant's arguments filed on 02/06/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "While Applicant respectfully maintain that the specification provides written description for the claimed invention, the claims have been amended to recite the embodiments indicated in the Office Action to be sufficiently disclosed, rendering moot the rejection. Accordingly, Applicants respectfully request removal of the rejection under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention of claims 1 and 3-11."

It remains the Examiner's position that the specification does not describe a method of measuring any "chemical marker" expressed by fibroblasts to detect IgG-activated fibroblasts. The specification discloses only the measurement of RANTES and IL-16 as chemical markers of fibroblast activation. The term "chemical marker" encompasses a broad genus of indicators of fibroblast activation that don't necessarily have anything to do with Graves Disease such as increased expression of surface molecules or other normal cellular indicators of growth and differentiation. The specification has not adequately described the genus of all chemical markers for use in the claimed invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3 and 7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kendall-Taylor et al. (PTO-892 mailed on 06/27/2008; Reference U) for the same reasons as set forth in the Office Action mailed on 06/27/2008.

Applicant's arguments filed on 02/06/2009 have been fully considered, but are not found persuasive.

Applicant argues:

"Applicants respectfully traverse the rejection of claims 1-3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Kendall-Taylor et al., Journal of Endicronology (1990).

Kendall-Taylor, in a brief abstract, discuss a possible modulatory role of TAO IgG's on IGF-1 levels associated with extraocular myoblasts. Kendall-Taylor et al. do not teach or suggest the activation of fibroblasts by binding of disease specific IgG to the IGF- 1 receptor (IGF-1R). The IGF-1 receptor is not mentioned, directly or indirectly, in the short abstract.

Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. *See Schering Corp. v. Geneva Pharms., Inc.,* 339 F.3d 1373, 1379 (Fed. Cir. 2003); *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1267-69 (Fed. Cir. 1991). An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 457 F.3d 1293, 1306-07 (Fed. Cir. 2006); *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. and Research,* 346 F.3d 1051, 1054 (Fed. Cir. 2003).

To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *NetMoneyIN, Inc. v. VeriSign, Inc., 545* F.3d 1359, 1369 (Fed. Cir. 2008) (quoting Connell v. Sears, Roebuck and Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983)); see *also, e.g., In re Arkley, 455* F.2d 586, 587 (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference" (emphasis in original)).

Because Kendall-Taylor et al. do not teach or suggest the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R). The IGF-1 receptor is not mentioned, directly or indirectly, and no suggestion of a relationship between binding of TAO IgGs to the IGF-1R is found in the Kendall-Taylor abstract. Accordingly, Applicants respectfully request removal of the rejection of claims 1, 3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Kendall-Taylor et al., Journal of Endicronology (1990).

It remains the Examiner's position that Kendall-Taylor et al. anticipates the claimed method. The reference teaches the exact method steps recited in the claims. The claims require only obtaining an orbital or skin sample comprising fibroblasts and detecting the activation of fibroblasts by measuring a chemical marker expressed by activated fibroblasts. The claimed method teaches that any chemical marker expressed by activated fibroblasts obtained from a patient orbital or skin sample may be measured to detect Graves Disease. The claims do not require the active step of activating the fibroblasts with disease specific IgG to the IGF-1 receptor. The claims only require the detection of those fibroblasts and the claims recite that those fibroblasts may be detected using any chemical marker. Therefore, the method is inherently detecting fibroblasts that have been activated by disease specific IgG to the IGF-1 receptor. In addition, the title of the abstract teaches that the IGF-1 levels rise in response to Graves IgG. The specificity of the Graves IgG need not be taught or known to anticipate the claimed invention. The same method steps are being performed using the same patient sample, so the result is necessarily inherent. Applicant is attempting to rely on a previously unappreciated property of the method in order to make the method patentably distinct. Fibroblast activation by disease specific IgG to the IGF-1 receptor is an intrinsic property of the Graves IgG activated fibroblasts expressing IGF-I in Graves' Disease patients. See In re Cruciferous Sprout Litigation, 301 F.3d 1343, 64 USPQ2d 1202 (Fed. Cir. 2002).

8. Claims 1, 3 and 7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rotella et al. (IDS filed 11/04/2002) for the same reasons as set forth in the Office Action mailed on 06/27/2008.

Applicant's arguments filed on 02/06/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "Rotella et al. describes an assay for measuring the activity of autoantibodies active in causing ophthalmopathy and concludes that some but not all *TSH receptor* monoclonal antibodies have been found to duplicate the action of the autoimmune IgGs from the ophthalmopathy patients. Accordingly, Applicants respectfully request removal of the rejection of claims 1, 3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Rotella et al."

It remains the Examiner's position that Rotella et al. anticipates the claimed method. The reference teaches the exact method steps recited in the claims. The claims require only obtaining an orbital or skin sample comprising fibroblasts and detecting the activation of fibroblasts by measuring a chemical marker expressed by activated fibroblasts. The claimed method teaches that any chemical marker expressed by activated fibroblasts obtained from a patient orbital or skin sample may be measured to detect Graves Disease. The claims only require the detection of those fibroblasts and the claims recite that those fibroblasts may be detected using any chemical marker. Therefore, the method is inherently detecting fibroblasts that have been activated by disease specific IgG to the IGF-1 receptor. In addition, the reference teaches activation of fibroblasts using Graves IgG. The specificity of the Graves IgG need not be taught or known to anticipate the claimed invention. The same method steps are being performed using the same patient sample, so the result is necessarily inherent. Applicant is attempting to rely on a previously unappreciated property of the method in order to make the method patentably distinct. Skin fibroblast activation by Graves disease specific IgG to the IGF-1 receptor is an intrinsic property of the Graves IgG activated fibroblasts expressing collagen. See In re Cruciferous Sprout Litigation, 301 F.3d 1343, 64 USPQ2d 1202 (Fed. Cir. 2002).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weightmann et al. (PTO-892 mailed on 06/27/2008; Reference V).

Weightmann et al. teaches a method of detecting Graves' disease in a human patient comprising (a) obtaining a biological sample comprising fibroblasts (3T3 cell line, tissue) from the patient (mouse), and (b) detecting in said biological sample (3T3 cell line) the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease in the human patient (IgG donor) ; wherein the detecting is accomplished by measuring the level of a chemical marker (presence of 135kDa band) expressed by said IgG-activated fibroblasts in said biological sample (3T3 cell line, tissue), wherein an elevated level of the marker (presence of 135kDa band) compared to the control indicates presence of said IgG-activated fibroblasts (In particular, abstract). The reference also teaches that Graves Disease is associated with opthalmopathy and modified IGF-I binding on orbital fibroblasts.

The claimed invention differs from the prior art in the recitation of "obtaining an orbital or skin sample containing fibroblasts from the patient" in claim 1.

It would be obvious to one of ordinary skill in the art, given the teachings of Weightmann et al. to use fibroblasts obtained from an orbital or skin sample containing fibroblasts from the patient that is the source of the Graves Disease IgG since the reference teaches that IgG from Graves Disease patients targets the IGF-I receptor on mouse fibroblasts and induces the fibroblasts to express a 135 kDa chemical marker. One of ordinary skill in the art would have a high expectation of success in inducing expression of the same 135 kDa chemical marker as a result of the activation of the fibroblasts through the IGF-I receptor on fibroblasts from the donor of the Graves IgG, particularly since the reference teaches that Graves Disease is associated with opthalmopathy and modified IGF-I binding on orbital fibroblasts.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

11. Claims 1, 3-7 and 9-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Rotella et al. (IDS filed 11/04/2002) in view of Sciaky et al. (IDS filed on 11/04/2002) and Lim et al..(IDS filed on 11/04/2002) for the same reasons as set forth in the Office Action mailed on 06/27/2008.

Applicant's arguments filed on 02/06/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> Neither Sciaky et al. nor Lim et al. cure the deficiencies of the primary references discussed above. In particular, the combination of Rotella et al. in view of Sciaky et al. and Lim et al., does not teach or suggest the method of detecting Graves' disease in a patient by obtaining an orbital or skin sample including fibroblasts from the patient, and detecting the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1 R) relative to a control wherein an increased presence of IgG-activated fibroblasts compared to the control indicates Graves' Disease, and wherein fibroblast activation is determined by measuring the level of a chemical marker expressed by the IgG-activated fibroblasts or by measuring T cell migration towards the fibroblasts in the orbital or skin sample. Rotella has particular deficiencies as disclosed above. Sciaky et al. and Lim et al. do not address any of the deficiencies of the primary references.
>
> As previously held by the Federal Circuit and reiterated by the KSR Court, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn,* 441 F.3d 977,988 (CA Fed. 2006) (emphasis added). The U.S. Patent and Trademark Office recently promulgated guidelines for Examiners in making obviousness determinations in view of the U.S. Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57,526 (2007) ("Guidelines") One important feature of the Guidelines is an *explicit requirement* that an Examiner provide articulated reasons for the factual determinations underlying an asserted *prima facie* case of obviousness. This focus is consistent with the rule set down in the KSR decision that a fact finder must provide "reasons" why an invention would have been obvious to one of ordinary skill in the art.." *KSR* at 1741. In explicating this aspect of the Supreme Court's decision, the Guidelines set forth explicit factual findings that an Examiner must articulate to support an obviousness rejection. For an obviousness rejection based on a rationale of combining references, the Examiner *is required to articulate* the following: (1) a finding that the prior art included *each element claimed;* (2) that one of ordinary skill in the art could have combined the elements by known methods, and that in combination each element merely would function as it did separately; (3) one of ordinary skill in the art would have recognized that the results of the combination were predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Fed. Reg. at page 57,529. In the current Office Action, the Examiner lumps together four primary references that are *each* alleged to render obvious the claimed invention in combination with the cited secondary references. This amounts to four separate obviousness rejections supported by primary references with very different teachings. The Examiner has not articulated a reasoned obviousness rejection as required by the Guidelines tailored to each reference. In addition to this procedural deficiency in the rejection, the substantive deficiency is that neither Sciaky et al. nor Urn et al. cure the deficiencies of the primary references discussed above. In particular, the combination of Rotella et al. in view of Sciaky et al. and Lirn et al., does not teach or suggest the claimed methods.

It is the Examiner's position that she has not performed any kind of procedural deficiency with regard to the rejection set forth in the Final Rejection. Further, the Examiner has indeed

articulated her reasoning explicity, contary to Applicant's assertion. The Sciaky et al. and Lim et al. references can be applied to Rotella to arrive at the claimed invention because Sciaky et al. teaches that human fibroblasts express chemotactic cytokines IL-16 and RANTES upon activation which recruits T cells to the site of inflammation (In particular, whole document) and Lim et al. teaches that IL-16 and RANTES are chemoattractants for T cells and chemotaxis of T cells can be measured as an indication of the presence of IL-16 and RANTES (In particular, abstract, 'Lymphocyte Chemotaxis' section). Sciaky et al. and Lim et al. can be applied to Rotella, which measures the activation of fibroblasts in a different way. It would have been obvious to one of ordinary skill in the art at the time of invention to measure IL-6 and RANTES produced by fibroblasts as an additional indicator of fibroblast activation induced by IgG from Graves patients because Rotella et al. is directed to measuring the activation of fibroblasts in response to IgG from Graves Disease patients. In addition to the activation markers measured in Rotella et al., it would have been obvious to measure Il-16 and RANTES because Sciaky et al. teaches that chemotactic cytokines IL-16 and RANTES are expressed upon activation. It would have been obvious from the teachings of Lin et al. to detect IL-16 and RANTES expression by measuring T cell migration. From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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September 30, 2009
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